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Case report

# Bilateral chemodectoma: Medicolegal considerations on a case report of aeromedical concern

Angelo Landolfi MD, Aerospace Forensic Medicine [a,*], Arianna Giovannetti MD, Forensic Medicine [b], Paola Mancarella MD, Forensic Medicine [c], Stefano Conti MD, Aerospace Forensic Medicine [c], Fabio Morgagni MD, Aerospace Cardiology [a], Claudio De Angelis MD, Aerospace Cardiology [d]

[a] Italian Air Force Logistic Command, Flight Test Centre, Aerospace Medicine Department, Pratica di Mare, Via di Pratica di Mare 45, 00040 Rome, Italy
[b] Department of Anatomical, Histological, Legal Medical and Orthopaedic Sciences, Faculty of Medicine and Psychology, Sapienza University, Via di Grottarossa, 1035 Rome, Italy
[c] Department of Anatomical, Histological, Legal Medical and Orthopaedic Sciences, Faculty of Medicine and Pharmacology, Sapienza University, Viale Regina Elena 336, Rome, Italy
[d] Italian Air Force Medical Corps, Via Piero Gobetti 2, IML Roma, Italy

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ABSTRACT

The authors describe a case of bilateral carotid chemodectoma occurring in a military pilot who was assessed and evaluated in terms of aeromedical and medico-legal aspects for his fitness to fly. In view of the lack of specific guidelines and/or regulations, both national and international, we choose to follow a multidisciplinary clinical approach that included aero-physiological tests in the hypobaric chamber, in order to identify a standard protocol that could be used as reference for similar future cases, where this kind of assessment is necessary.



## 1. Introduction

In the present study the authors analysed a specific clinical case of a military young pilot suffering from a rare pathology, carotid paraganglioma (chemodectoma), which is not specifically included in the national and international regulations for the assessment of the fitness to fly. The aim of this study was to establish, for future reference, a diagnostic guideline to be used as standard protocol for the assessment of fitness to fly in similar cases.

It should be pointed out that the presence of conditions, believed to be unfavourable for the fitness to fly status, is ground for failure already during the first medical assessment and, if these conditions are cause of impediment for the specific tasks of the pilot, they can be ground for unfitness status also for the personnel already on duty, in accordance to the Italian Ministerial Decree 16 of September 2003: "List of imperfections and disabilities that are cause of unfitness to perform aero-navigation services and criteria to be implemented for the assessment and evaluation for fitness purposes". Some medical conditions are specifically addressed and listed in the following selection: "... past or recent medical history of any pathology that may progress in a disabling condition ... dysmorphism ... proteic-energy malnutrition (hyponutrition, hypernutrition, obesity, thinness) and local and systemic trophism alterations[e] ... central nervous system disorders ... peripheral nervous system disorders ... cranial-encephalic concussions, cranial fractures, vertebral fractures, spinal cord injuries and their outcomes ... current or past history of epilepsy[f] ... single seizure episodes[g] ... ECG parossistic abnormalities ... hypothalamous–hypophysis axis disorders ... gonad disorders ... cortical and medullar adrenal gland disorders ... thyroid, parathyroid and mineral metabolism disorders ... poly-endocrine syndromes ... ".

However, for the pathology of interest in this study, no guidelines are reported in national and international regulations;

* Corresponding author. Tel.: +39 06 91292547; fax: +39 06 91292075.
*E-mail addresses:* angelolandolfi@tiscali.it, angelo.landolfi@aeronautica.difesa.it (A. Landolfi), giovanetti.arianna@yahoo.it (A. Giovannetti), paola.mancarella@libero.it (P. Mancarella), stefano.conti@uniroma1.it (S. Conti), fabio.morgagni@am.difesa.it (F. Morgagni), claudio.deangelis@am.difesa.it (C. De Angelis).

[e] " In the case of overweight, a global assessment of cardiovascular risk will be performed on the personnel on duty,".
[f] "Always cause of unfitness to any role concerning flight activity, even if past or current but not requiring medication".
[g] "Cause of unfitness for pilots, sailors and aero-rescuers".

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therefore, given its peculiarity, the case has required a series of essential multidisciplinary assessments, including aero-physiological tests in hypobaric chamber.

## 2. The case

### 2.1. Subject

A 29-years-old male pilot was referred to the ItAF Aeromedical Institute for off frequency assessment of fitness to fly after rescission of bilateral carotid chemodectoma previously discovered in a screening involving also his father and sister. A Doppler ultrasonography on December 2007 evidenced a highly-vascularized solid mass at the right carotid fork, sized 2.5 cm longitudinally (cranial-caudal) × 3 cm transversally. The CT scan of the neck revealed a bilobal mass at the right carotid fork with large enhancement in the artery phase and tendency to homogenize in the venous phase, and a smaller vascular mass of 0.8 × 0.4 × 0.9 cm at the left carotid fork.

The subject underwent surgery on January 2008 in order to remove the right tumour. The mass was taken away and the right external carotid was closed at the fork, while the right internal carotid and the X and XII cranial nerves were left intact since they were not involved in the tumour. Four months later, a surgery was performed on the left to remove the mass including also all satellite lymph nodes.

The histological diagnosis was finally left carotid paraganglioma (chemodectoma) with low proliferation index and low mitotic index with aspecific reactive lymphadenitis.

In November 2010, due to relapse of the right chemodectoma, the subject underwent an intra-arterial chemoembolization. This resulted also in a mild damage of the XII cranial nerve resulting in right deviation of the tongue and impaired swallowing due to hypopharyngeal ataxy, and mild right palpebral ptosis with myosis and enophthalm. The latter was found resolved six months after.

The subject has been apparently in good health conditions. He resulted fit to fly at each visit in the last five years and attended to his flight duty as combat ready pilot on multiple crew turboprop aircraft (Breguet 1150 Atlantic).

### 2.2. Pathological findings

Paragnagliomas are clusters of neuroepithelial cells containing citoplasmic neurosecretory granules, which originate from the neural crest. The highest number of cases reported in literature refers to neoplasiae, generally benign, located at the carotid body and/or the jugular-tympanic ganglion, although other anatomical locations have also been reported.

In particular, the carotid paraganglioma is a rare tumour (its incidence in post-mortem studies is 0.01% and its incidence in all tumours is <0.5%; 1 case every 30,000 people per year) slow growing, that develops at the carotid body, a chemoreceptor organ localised at the carotid fork. Such anatomical structure (carotid body) is part of the extraadrenal paraganglia system that is a multicentre system, associated with the autonomous nervous system, formed by many microscopic organels and by groups of cells symmetrically and segmentally distributed, in the para-axial and partially in the peripheral region of the trunk and the neck.

It is equally distributed among sexes, and it affects mainly middle aged people (age range 25–75 years, mean 45 years); however, younger age cases have also been described.[1] Familiality has been postulated in many scientific papers: indeed, according to some authors (and as our case would confirm) a dominant autosomic inheritance with incomplete penetrance is likely.[2] Some studies have outlined a particular geographical distribution: Peruvian Andes, Colorado, Mexico City.

This seems to confirm the hypothesis by which hyperplasia, induced by chronic exposition to hypoxia, can lead to neoplastic transformation of the carotid paraganglium. Other conditions that expose a subject to chronic hypoxia, like in smokers, COPD patients, cardiopathy patients, are also predisposing the subject to develop glomic tumours.[3]

However, due to the risk of adrenergic crisis caused by catecholamines release, the risk of stroke by the compression or infiltration of carotid vessels, or due to the risk of distant metastases, surgical removal is considered necessary under the current guidelines.

Moreover, this type of tumour has a specific neurosecreting activity in 5% of cases; therefore, it is always necessary to perform the dosage of thyroid hormones, urinary and plasmatic catecholamines, urinary metanephrines, vanillymandelic acid, homovanillic acid and 5-HIAA.

Histologically it is formed by electrically coupled cells with features similar to SNP neurons. Chromaffin-like cells (type I glomic cells) and glial-like cells (type II glomic cells) can be distinguished. Carotid bodies are perfused with high flux by collaterals of the occipital artery (2 l/min/100gr; artery-venous difference in $O_2$: 0.15 ml %).

From a physiological point of view the carotid bodies respond to: $\downarrow PpO_2$, $\uparrow PpCO_2$ and $\downarrow$pH of artery blood. Because of the elevated haematic flux, glomic cells are exposed to artery $PpO_2$ and are able to detect its minimal variations. The activation of afferent fibres is mediated by the release of dopamine. The afferent chemoreceptors fibres are active at normal $PpO_2$ (95–100 mmHg) and their release frequency increases considerably following reductions of $PpO_2$ below 60–70 mmHg (values for which the Hb $O_2$ saturation rapidly decreases).

Chemoreceptor response is translated in an increase of pulmonary ventilation, exerted by an increase in both deepness and frequency of breathing. The increase in ventilation caused by the decrease of $PpO_2$ is mediated by a simultaneous increase of $PpCO_2$ and reduction of pH. Response to $PpCO_2$ activated by peripheral chemoreceptors is less potent than the response dependant on central chemoreceptors, even if the stimulation of peripheral chemoreceptors is more rapid. Finally, peripheral chemoreceptors can be stimulated also by an increase of circulating blood temperature, a reduction of the haematic flux of the glomus and a drop of systemic artery pressure.[4]

### 2.3. Aeromedical investigation

In order to perform a comprehensive evaluation, both aeromedical and medico-legal, of the fitness to fly that would consider the specific abilities necessary for this profession, we adopted a multidisciplinary approach, able to include strictly technical aspects of hypobaric exposure together with the physiopathological conditions of our clinical case.

The subject was studied from a medical point of view at the ItAF Aeromedical Institute where he received a complete clinical evaluation. The investigation proceeded with further aeromedical tests at the ItAF Aerospace Medicine Department in order to assess whether the pilot could be safely exposed to the flight challenges.

The first extensive evaluation was conducted after the first surgical operation. An Head-Up Tilt-Test without pharmacological enhancement gave no abnormal results. The 24-h Holter electrocardiogram and the ambulatory recording of blood pressure were normal. Due to the expected impairment in the tolerance to hypoxia in patients with carotid glomus denervation the subject underwent an exposure to simulated high altitude in hypobaric chamber with a standard training profile.[5] This consisted in two hypoxia exposures (see Fig. 1), respectively at 7620 m (25,000 ft) for

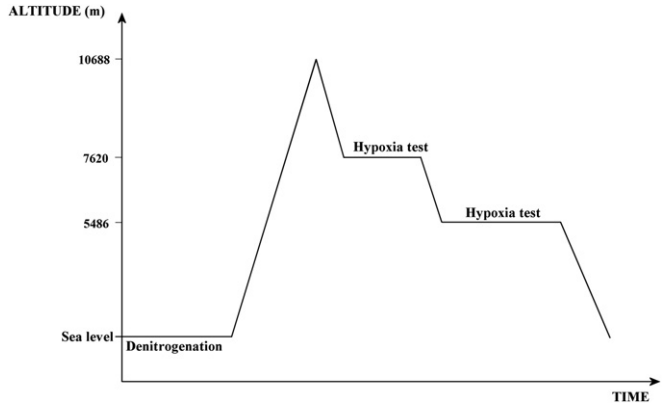


**Fig. 1.** The hypobaric chamber profile used for hypoxia demonstration at different altitude.

two to 4 min and at 5486.4 m (18,000 ft) for ten to 20 min. A rapid decompression demonstration consisting in a sudden rise starting at 2438.4 m (8000 ft) and ending at 6705.6 m (22,000 ft) in less than 3 s. The subject responded normally at 7620 m (25,000 ft), at 5486.4 m (18,000 ft) and during rapid decompression with a normal compensatory response to hypoxic hypoxia. The subject was studied again after the second surgical resection of the chemodectoma. The Head-Up Tilt-Test, the 24-h ECG Holter, and the blood pressure monitoring were normal. The subject was exposed to the hypobaric chamber profile as previously and he experienced a "vagal-like syndrome" with the occurrence of marked bradycardia and loss of consciousness. Few months after, the subject received his third aerophysiological evaluation. No different results came from Head-Up Tilt-Test, 24-h ECG Holter and blood pressure monitoring. A symptom-limited cardiopulmonary exercise test revealed a decreased ventilatory response and quite low oxygen consumption without any other abnormality. An altitude profile up to 4572 m (15,000 ft) was designed in order to reproduce the flight profile of the Bregeut 1150 Atlantic, with very slow ascent and descent rates never exceeding 152.4 m/min (500 ft/min). The subject, who had been previously briefed, appropriately detected the symptoms of hypoxia at 3657.6 m (12,000 ft) and was able to respond autonomously with restoring the oxygen supply.

## 3. Discussion

The medico-legal assessment of pilots and flight crewmembers has two main purposes: the first is to assess the functional ability of the pilot and to ascertain whether he is physically able to exercise safely the privileges of his licence in all routine and emergency situations; the second is to assess his risk of incapacitation during the period of validity of the medical certificate for which he has applied.

In view of what reported so far, it appears clear that this pathology is potentially able to impair the adaptation to altitude, which is paramount for a pilot.

In order to define the most suitable medico-legal approach to determine the fitness to fly for a pilot, we examined our clinical case under the current Italian regulation for the medical certification for military flights, Ministerial Decree 16 of September 2003: "List of imperfections and disabilities that are cause of unfitness to perform aero-navigation services and criteria to be implemented for the assessment and evaluation for fitness purposes". Considering that this pathology is rare, and it is not provided for in the above mentioned national regulation, we have considered also the current International Regulation for Civil Aviation (JAA JAR-FCL 3 – Flight Crew Licensing (medical) Amendment 5) where again it was not possible to find direct references for the assessment of fitness to fly in subjects affected by chemodectoma with bilateral ablation of carotid bodies.

From data available in literature it emerges that the ventilatory adaptation response to normocapnic hypoxia can be abolished in subjects that had undergone a bilateral resection of the carotid bodies, while the ventilatory response to hypercapnia is only reduced.[6] Moreover, cases of associated carotid baroreceptor denervation have been observed as complication to surgery. Depending on the extension of the denervation itself, they can develop into a temporary loss of the ability to short term adaptation of systemic artery pressure with increase in variability and restoration time ranging between 3 and 32 weeks from surgery; this is due to the vicarious action of other systems, that is, a baroreflex failure that can occur in several clinical presentations; in the acute phase the most common presentation is an hypertensive crisis. In the weeks following surgery a volatile hypertension can occur and orthostatic hypotension periods can last for many years. In rare cases, a malignant vagotony can occur, with severe bradycardia, hypotension and sinus arrest episodes.[7]

In the case discussed here, the subject did not present symptoms of baroreceptor dysfunction in any occasion with the methods used (AP Holter monitoring, FC, Head-up tilt test, cardiovascular tests), although specific pharmacological tests with vasopressure and/or vasodilator agents have not been performed (nitroprussiate and/or phenylephrine tests). Aerophysiological aptitude tests carried out in hypobaric chamber at the Aerospace Medicine Department have shown, in the 5486.4 m (18,000 ft) and 7620 m (25,000 ft) profiles, an inappropriate bradhycardia with loss of adaptive ventilation response during the administration of the hypoxic stimulus. Conversely, in the slow decompression profile, the subject has shown a gradual adaptation up to 3657.6 m (12,000 ft).

Further evaluations with the human centrifuge test would have been useful for this specific pathology. This would have allowed to study a possible deficit in +Gz accelerations tolerance. However, we decided against this test for two reasons. First of all, the unavailability in Italy of such device (that is used for training purposes in other European countries and in the United States) and secondly because the pilot examined was operating on planes with low +Gz load. To support our decision, we later observed that, following his return to service on planes with low +Gz load, he did not show any disorders linked to the acceleration factor.

## 4. Conclusion

By the administration of the above described tests, the functional respiratory impairment of the subject was confirmed. This limitation, although was reason of vulnerability in terms of defence against hypobarism, did not modify the ability of the subject to recognize the symptoms of hypoxic hypoxia, nor has abolished the possibility to increase ventilation with other mechanisms (the ventilation increase mediated by the central chemoreceptor and by the voluntary component).

In conclusion, in view of what found with the different tests performed and in consideration of the standard levels of cabin pressurization during profiles typical of the Antisom Atlantic, our medico-legal authorities have decided to give the examined subject a favourable opinion for the fitness to fly, limited in time and modalities, i.e. they have allowed the possibility of a specific typology of piloting cd with double command and avoiding aereotactical jets, allowing to safeguard the professional experience already acquired by instrumental close controls performed in order to detect as early as possible any further functional limitation.

This medical-legal judgement find its support in the art.3 "*flexibility clause*" of the Ministerial Decree 16.09.2003: "... in the formulation of judgements the effective performed activity should be considered and it should also be taken into account that experience can compensate possible functional deficits...when grading fitness to fly...".

Finally, we can conclude that the multidisciplinary approach chosen and used at the Aerospace Medicine Department, as described in this study, with the profiles in the hypobaric chamber that have been tested, and in view of the lack of established data in national and international literature, can be employed as a reference model for the aeromedical and medico-legal management of possible future similar cases.

*Ethical approval*

This work is written in accordance with The Code of Ethics of the World Medical Association for experiments involving humans.

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*Contributors*

Angelo Landolfi has managed hypobarc chamber test of the military pilot and medicolegal considerations.

Claudio De Angelis and Fabio Morgagni have managed all cardiac function tests.

Paola Mancarella, Stefano Conti and Arianna Giovannetti have managed the treatment of forensic science.

*Submission declaration*

The work described has not been published previously.

This publication is approved by all authors and by the responsible authorities where the work carried out.

If accepted it will not be published elsewhere without the written consent of the copyright content.

*Conflict of interest*

The authors declare that they have not conflict of interest and did not receive any financial and material support for this work.

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